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Syphilis testing among spouses of patients with syphilis in Japan: an epidemiological study using an administrative claims database

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First edition

1 **Title page**

2

3 **Syphilis testing among spouses of patients with syphilis in Japan: an epidemiological**
4 **study using an administrative claims database**

5

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16

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1 Introduction

2 Incidence rates of syphilis, a sexually transmitted infection (STI) caused by *Treponema*
3 *pallidum*, is increasing in high-income countries.^{1,2} In the United States and Western Europe,
4 there has been a sharp increase in cases of primary and secondary syphilis primarily among
5 men who have sex with men.^{1,2} In Japan, the incidence of syphilis increased from 883 in 2012
6 to 4564 in 2016, and the majority of syphilis cases were among heterosexual men and
7 women.³ In addition, among young women, the number of primary and secondary syphilis
8 cases reported in Japan has increased rapidly since 2014, with the proportion of women
9 among those aged 20–29 years increasing from 31.1% in 2014 to 54.5% in 2018.^{4,5} Syphilis
10 in women of reproductive age, especially those in their 20s and 30s, can lead to mother-to-

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11 child transmission during pregnancy and adverse pregnancy outcomes, including stillbirth,
12 neonatal death, low birth-weight, and prematurity. Therefore, public health strategies need to
13 be strengthened to prevent the spread of syphilis, especially through heterosexual contact
14 among women of reproductive age.

15 Partner notification (PN) is one of the most critical public health interventions for
16 prevention of the spread of STIs. PN is a means for informing the sex partners of patients
17 diagnosed with an STI that they have been exposed to an STI and for providing testing and
18 treatment. There are five main PN strategies: (1) patient referral, (2) assisted partner
19 notification, (3) expedited partner therapy, (4) provider referral, and (5) contact referral.⁶ To
20 eradicate infection and prevent re-infection, many high-income countries adopt multiple

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21 types of PN in their programs for syphilis control.⁷⁻¹⁰ However, of these strategies, only
22 simple patient referral, which entails a physician advising patients that their partner should
23 be tested, is available in Japan. This is primarily because personal information that can
24 identify patients with syphilis is not included in the items reported by physicians to local
25 public health centres under the Infectious Diseases Act. As a result, staff working in local
26 public health centres cannot interview patients or notify their partners. With the substantial
27 increase in the incidence of syphilis, PN has become a more critical means of controlling
28 syphilis; therefore, public health policymakers need to understand the effectiveness of simple
29 patient referral in Japan. However, it remains unclear, whether contacts of patients with
30 syphilis are notified that they are at risk of syphilis transmission, and whether contacts receive

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31 treatment for syphilis.

32 Infection control policies should be reorganised in response to the growing syphilis

33 epidemic.¹¹ If investigations reveal that few contacts with syphilis have been screened

34 through simple patient referral, Japanese policymakers may try to modernise current

35 infection control strategies to provide a more practical partner service. In the present study,

36 we aimed to determine the proportion of patients whose spouses, particularly women of

37 reproductive age, underwent syphilis testing after their partners were diagnosed with syphilis,

38 using an administrative claims database.

39

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40 **Materials and methods**41 **Study design and data source**

42 We conducted a retrospective descriptive study that used a large administrative claims
43 database maintained by the Japan Medical Data Center (JMDC, Tokyo, Japan). The analysis
44 covered claims between January 2010 and December 2017. The JMDC collects data
45 regarding inpatient, outpatient, and pharmacy insurance claims of members of various health
46 insurance associations that cover employees in large companies, and the spouses and
47 dependents of these members.^{12,13} The database includes clinical and procedural information
48 with an encrypted personal identifier, sex, year and month of birth, medical diagnosis codes
49 according to the International Classification of Diseases 10th Revision (ICD-10), the drug

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50 codes according to the World Health Organization (WHO) Anatomical Therapeutic
51 Chemical system, and the medical procedure codes. The database also includes anonymised
52 family identification codes and insurance coverage periods, which enabled us to identify
53 husband-wife relationships according to the time period. Due to the JMDC's privacy policy,
54 medical diagnosis codes, drug codes, and medical procedure codes linked with human
55 immunodeficiency virus infections were not stored in the database and were not provided to
56 the investigators.

57 The study was conducted in accordance with the Declaration of Helsinki, and was
58 approved by the Institutional Review Board of the University of Kyoto (No. R1563). Due to
59 the anonymous nature of the data, the requirement for informed consent was waived in

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60 accordance with the Japanese ethical guidelines.

61

62 **Syphilis testing in Japan**

63 Syphilis testing in Japan is divided into those tests that are covered by health insurance and

64 those that are not. The tests covered by health insurance are performed at medical institutions

65 on patients with symptoms or suspected infection. In addition, tests for infection, including

66 syphilis testing, are performed before invasive treatment, such as surgery. Conversely, the

67 tests not covered by health insurance include free tests conducted at local public health

68 centres and universal prenatal syphilis screening at an early gestational age. Routine annual

69 general health check-ups do not include syphilis testing.

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70

71 **Selection of index patients with syphilis and their spouses**

72 We identified index patients who were newly treated for syphilis between January 2010 and

73 December 2017. The dates of syphilis treatment were determined based on the month of the

74 first prescription of antibiotics for syphilis. New treatment of syphilis was defined as (1)

75 having a definitive diagnosis of syphilis (ICD-10 code: A51, A52, or A53); (2) prescription

76 of antibiotics for syphilis; and (3) performance of syphilis testing as both nontreponemal and

77 treponemal tests in the month of antibiotic prescription, or in the month preceding antibiotic

78 prescription. Antibiotics for syphilis were defined according to the guidelines of the Japanese

79 Society for Sexually Transmitted Infections (amoxicillin, ampicillin, minocycline,

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80 doxycycline, azithromycin, acetylspiramycin, ceftriaxone, and benzylpenicillin).^{14,15} The
81 guidelines suggest using amoxicillin or ampicillin 500 mg three times daily orally.
82 Benzathine penicillin G, which is recommended by the WHO guidelines for the treatment of
83 *Treponema pallidum* infection,¹⁶ was not included in the list because it has not been available
84 in Japan.

85 We excluded patients aged <20 years because this database only identified married
86 pairs, and adolescents are unlikely to be married. To increase the accuracy of the definition
87 of newly treated syphilis by excluding patients treated previously, we required continuous
88 enrolment in the health insurance plan for at least 6 months before the syphilis treatment
89 started. We also excluded patients who underwent surgery, blood transfusion, gastrointestinal

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90 endoscopy, or coronary angiography during the index month because syphilis testing may be
91 performed as a screening test for these procedures.

92 We identified the spouses of index patients using anonymised family identification
93 codes. If both the husband and wife were treated for syphilis, we chose the spouse who was
94 treated first as the index patient. To determine whether the spouse was tested after treatment
95 of the index patient, we included only spouses who were enrolled in the health insurance plan
96 for at least three months after the index patient started treatment.

97

98 **Outcomes**

99 The outcome of interest was spousal syphilis testing within three months of the index patient

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100 starting syphilis treatment. Spousal syphilis testing was defined as either nontreponemal or
101 treponemal testing for syphilis according to the medical procedure codes. Because the dataset
102 used in this study did not include information on whether the index patient notified his or her
103 spouse, spousal notification was not an outcome of this study.

104

105 **Other variables**

106 We extracted information on index patient demographic characteristics, including age (20–
107 44 and 45–74 years), sex, and clinical characteristics of previous STI diagnoses according to
108 the ICD-10 codes (including gonorrhoea (A54), chlamydia (A55–A56), genital herpes (A60)),
109 and psychiatric disorders (schizophrenia, schizotypal and delusional disorders: F20–F29 and

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110 mood disorders: F30–F39). Clinical data within 3 months preceding the index month were
111 also assessed. We also recorded the provider type (clinic and hospital) and the year of syphilis
112 treatment (2010–2011, 2012–2013, 2014–2015, and 2016–2017). In Japan, clinics are
113 defined as medical institutions with 19 beds or fewer, and hospitals as those with 20 beds or
114 more. Spousal demographic characteristics included age (20–44 and 45–74 years) and sex.

115

116 **Statistical analyses**

117 Firstly, descriptive statistics were calculated for the basic demographic and clinical variables
118 of the index patient. Secondly, male-female and female-male contacts were analysed
119 separately. We calculated the proportion of patients with newly treated syphilis during the

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120 study period whose spouses had undergone syphilis testing within 3 months of treatment

121 initiation. Associations between the characteristics of index patients and their spouses and

122 performance of spousal syphilis testing were evaluated using Fisher's exact test. The trend

123 in the proportion of spousal syphilis testing during the study period was assessed using the

124 Cochran-Armitage trend test. Thirdly, to evaluate the prevention of congenital syphilis, we

125 determined the proportion of men married to women aged 20–44 years who had undergone

126 a spousal syphilis test. This age range was chosen because approximately 99% of mothers in

127 Japan gave birth when they were between the ages of 20 and 44 years.¹⁷ Probability values

128 for statistical tests were two-tailed, and p-values <0.05 were considered to be statistically

129 significant. All statistical analyses were performed using SAS version 9.4 for Windows (SAS

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130 Institute, Cary, NC, USA).

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131 **Results**

132 During the study period, 217 pairs of patients with syphilis and their spouses met the
133 inclusion criteria (Figure 1). The characteristics of the index patients with syphilis are shown
134 in Table 1. Between 2010 and 2013, 10 or fewer index patients were diagnosed with syphilis
135 per year; however, during the period 2014–2017, the number of index patients increased each
136 year from 23 in 2014 to 75 in 2017.

137 Overall, 29 of 217 spouses (13.3%) underwent syphilis testing within 3 months of
138 the index patient's new syphilis treatment (Table 2). The proportion of spousal syphilis
139 testing was 12.6% among the wives of male index patients, and 17.1% among the husbands
140 of female index patients, respectively. Among male index patients, the proportion whose

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141 wives were tested was higher among those aged 20–44 years than among those aged 45–74
142 years, whereas among female index patients, the proportion whose husbands were tested did
143 not differ by age group. The proportion of spouses tested did not differ significantly
144 according to STI history or psychiatric disease history. The spouses of all 12 index patients
145 who were treated at a hospital were tested for syphilis.

146 Although not significant, among male index patients, the wives of those aged 20–44
147 years were more likely to undergo syphilis testing than those aged 45–74 years. Similarly,
148 the wives aged 20–44 years were more likely to undergo syphilis testing than those aged 45–
149 74 years. The proportion of spousal syphilis testing declined from 37.5% in 2010–2011 to
150 9.5% in 2016–2017 (P for trend = 0.01).

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151 Table 3 shows the proportion of wives aged 20–44 years who underwent spousal
152 syphilis testing. The proportion of spousal syphilis testing was higher among index patients
153 aged 20–44 years than among those aged 45–74 years. The proportion of spousal syphilis
154 testing decreased significantly between 2010–2011 and 2016–2017 (P for trend = 0.03).

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155 **Discussion**

156 To the best of our knowledge, the present study is the first in Japan to describe partner syphilis
157 testing using an administrative claims database. Less than one in seven spouses of index
158 patients with syphilis underwent syphilis testing within three months after their spouse was
159 treated. In the subgroup of wives aged 20–44 years, who constitute women of reproductive
160 age, approximately one-fifth of underwent syphilis testing within three months, and the
161 proportion tested decreased significantly between 2011–2012 and 2016–2017. Another
162 unique feature of our study is the use of existing health insurance claims data without the
163 collection of primary data. We determined whether partners were tested using claims data
164 which identified married couples.

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165 In a questionnaire survey of physicians conducted in Japan in 2006, 17.5% of
166 partners of patients, who were diagnosed with an STI such as chlamydia or gonorrhoea, were
167 examined or treated for STIs.¹⁸ Recent studies conducted in the United States reported that
168 63–81% of named partners were tested for syphilis as a result of disease intervention
169 specialist investigations.^{19–21} In randomised controlled trials of patients with gonorrhoea or
170 chlamydial infection, conducted in the United States, 35–52% of named partners either tested
171 negative or were treated through simple patient referral.^{22,23} Another previous randomised
172 controlled trial among men and women with chlamydial infection found that 45% of named
173 partners were treated by simple patient referral.²⁴ Our study found that in Japan the proportion
174 of partners tested through simple patient referral was only 13% among married couples. This

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175 result is similar to the result of the previous study conducted in Japan, but is lower than those
176 of studies conducted in other countries. One possible reason for this difference may be that
177 physicians in Japan may not explain the necessity of spousal testing to patients more carefully
178 compared with those in other countries. Because PN services involving public health sectors
179 have not been not implemented in Japan, there may be a difference in physicians' interest
180 and practice in caring for partners. As a result, some physicians may not adequately inform
181 patients regarding the need for partner testing. In addition, because the present study was
182 conducted among married couples, disclosing a diagnosis of syphilis to a partner would have
183 revealed infidelity; therefore, patients may have been reluctant to disclose the diagnosis to
184 their spouse. These factors may partially explain the differences in the proportion of partners

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185 tested in our study and previous studies.

186 Patients may have difficulty in referring their partner for syphilis testing if the
187 physician advises, "Tell your partner that he/she needs to be tested." because patients are
188 hesitant to notify their partner due to guilt and stigma.²⁵ Therefore, public health specialists
189 need to support patients' efforts to communicate with their partners by helping them
190 understand the need to notify their partners and the possible adverse health effects of having
191 an untreated STI. In a retrospective observational study of PN of syphilis conducted in
192 Switzerland, patients diagnosed at a public university hospital were less likely to notify their
193 partner than those diagnosed at other institutions.²⁶ This difference may have been due to
194 differences in patient characteristics between institutions. In contrast, in our study, all 12

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195 spouses of index patients treated at hospitals were tested for syphilis. Because the health care
196 setting in Japan allows patients to visit any medical institution, it may be due to differences
197 between hospitals and clinics in the quality of PN, rather than differences in the
198 characteristics of the patient population.

199 Despite increased public interest in syphilis due to the increase in reported syphilis
200 cases, the present study showed that the proportion of wives aged 20–44 years who were
201 tested for syphilis declined during the study period. The Japanese Ministry of Health, Labour,
202 and Welfare has strengthened its prevention programs in order to increase public awareness.
203 This effort has included new types of health campaigns that use manga cartoons to target the
204 public in their 20s to 40s and increase opportunities for people to undergo STI testing.²⁷

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205 However, health information campaigns and a population-based intervention approach are
206 only effective among those who consider themselves to be at risk.²⁸ Therefore, the decrease
207 in spousal testing, despite health campaigns, may be due to an increased incidence of syphilis
208 in populations previously at low risk.

209 Our study has several limitations. Firstly, information about the syphilis stage of the
210 index patients was unavailable. Unlike the high infectivity of primary and secondary syphilis,
211 the transmission of late syphilis is unlikely; thus, screening contacts of patients with late
212 syphilis is generally unnecessary. However, even in patients with late-latent syphilis, it is
213 appropriate to screen long-term sex partners for syphilis.⁷⁻¹⁰ Because our study used marital
214 data, screening of spouses was advisable regardless of the syphilis stage of the index patient.

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215 Secondly, the nature of the marital relationship during the infectious period was unclear. If
216 the patient did not have sexual contact with the spouse during the infectious period, the
217 outcomes of spousal syphilis testing might be underestimated as the spouse did not need to
218 be tested for syphilis. In particular, it was estimated that more older couples had not had
219 sexual contact in the preceding two years compared with younger couples. Thirdly, selection
220 bias may limit the generalisability of our findings because the population of employees and
221 their spouses in the present study had a higher socioeconomic status than the overall
222 population at risk of syphilis. However, given that patients with syphilis are less likely to
223 notify casual partners than long-term stable partners,²⁹ the contacts of patients with syphilis
224 in Japan overall may be less likely to undergo screening than the population of our study.

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225 Fourthly, the small sample size of index patients precludes a multivariate analysis of partner
226 testing according to variables such as sex, age, clinical characteristics, or provider type.
227 However, the data used in the present study were from the largest database of information on
228 married couples that is currently available in Japan. To address the public health concern of
229 the rapid increase in the incidence of syphilis, our study provides timely results to public
230 health policymakers from a current database. Finally, spouses may have undergone syphilis
231 testing that was not covered by health insurance. People can visit specialised medical
232 institutions at relatively low prices under the Japanese health insurance system.^{30,31} Although
233 some local public health centres are trying to improve access to free syphilis testing, the
234 accessibility to free testing is generally poor. In addition, most syphilis cases have been

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235 reported from clinics and hospitals rather than from local public health centres.

236 Despite public health interventions to increase syphilis testing of contacts in Japan,³

237 only approximately one-seventh of spouses of patients who start syphilis treatment undergo

238 testing. The present study provides evidence that syphilis testing among contacts has been

239 low and has declined over the past eight years. Although surveillance and awareness-raising

240 have been intensified in Japan due to the recent surge in the incidence of syphilis, there is a

241 need to coordinate surveillance and field services that remain fragmented. Our findings

242 highlight the importance of introducing PN services that will result in higher partner testing

243 rates.

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247

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341 **Figure legends**

342

343 Figure 1. Flow diagram of the participant selection process

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Table 1. Characteristics of the index patients (n = 217).

Characteristics	n (%)
Age, years	
20–44	89 (41.0)
45–74	128 (59.0)
Female sex	35 (16.1)
STI history	
Gonorrhoea	6 (2.8)
Chlamydia	12 (5.5)
Genital herpes	19 (8.8)
History of psychiatric disorders	12 (5.5)
Age of spouse, years	
20–44	101 (46.5)
45–74	116 (53.5)
Provider type	
Clinic	205 (94.5)
Hospital	12 (5.5)
Year of syphilis treatment	
2010–2011	14 (6.5)
2012–2013	15 (6.9)
2014–2015	58 (26.7)
2016–2017	130 (59.9)

STI, sexually transmitted infection

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Table 2. Number and proportion of index patients whose spouses underwent syphilis testing according to patient characteristics

Variables	Male index patients		Female index patients	
	n = 182 (%)	P	n = 35 (%)	P
Overall	23 (12.6)		6 (17.1)	
Age, years				
20–44	13 (19.4)	0.062*	4 (18.2)	>0.99*
45–74	10 (8.7)		2 (15.4)	
History of STIs				
No	21 (13.9)	0.377*	4 (12.9)	0.128*
Yes	2 (6.5)		2 (50.0)	
History of psychiatric disorders				
No	21 (12.2)	0.617*	6 (18.2)	>0.99*
Yes	2 (20.0)		0 (0.0)	
Age of spouse, years				
20–44	14 (16.5)	0.181*	3 (18.8)	0.654*
45–74	9 (9.3)		3 (15.8)	
Provider type				
Clinic	14 (8.1)	<.0001*	3 (9.4)	0.003*
Hospital	9 (100.0)		3 (100.0)	
Years of syphilis treatment				
2010–2011	3 (37.5)	0.014†	2 (33.3)	0.547†
2012–2013	3 (25.0)		0 (0.0)	
2014–2015	6 (13.0)		2 (16.7)	
2016–2017	11 (9.5)		2 (14.3)	

*Fisher's exact test

†Cochran-Armitage test

STI, sexually transmitted infection

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Table 3. Syphilis testing among wives aged 20–44 years, according to the characteristics of the index patient

Variables	Number of spouses	Syphilis testing (%)	<i>P</i>
Overall	85	14 (16.5)	
Age of the index patient, years			
20–44	65	13 (20.0)	0.171*
45–74	20	1 (5.0)	
History of STIs			
No	69	13 (18.8)	0.290*
Yes	16	1 (6.3)	
History of psychiatric disorders			
No	81	13 (18.8)	0.520*
Yes	4	1 (25.0)	
Provider type			
Clinic	80	9 (11.3)	<0.001*
Hospital	5	5 (100.0)	
Years of syphilis treatment			
2010–2011	3	2 (66.7)	0.026†
2012–2013	6	2 (33.3)	
2014–2015	21	3 (14.3)	
2016–2017	55	7 (12.7)	

*Fisher's exact test

†Cochran-Armitage test

STI, sexually transmitted infection

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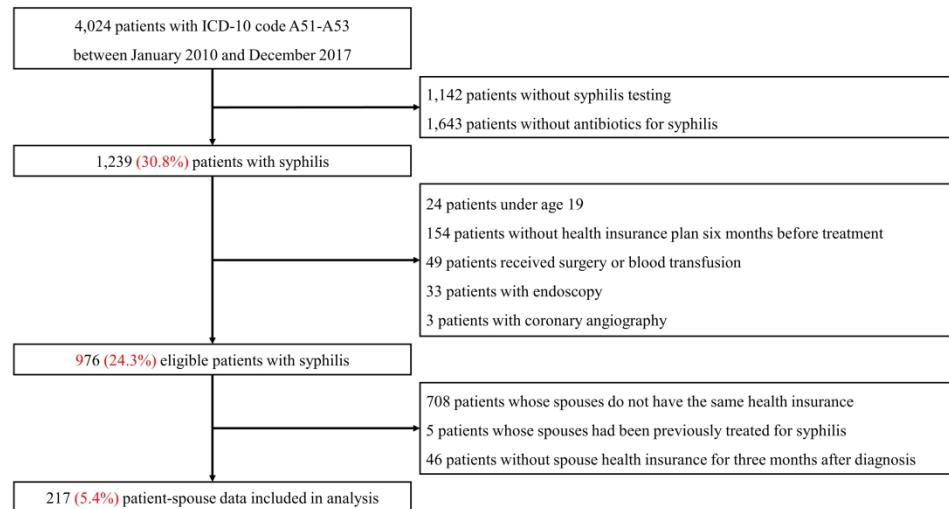


Figure 1. Flow diagram of the participant selection process.

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